IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Barta et al.
Serial No: 09/311,837
Filed: May 14, 1999
For: AROMATIC SULFONE HYDROXAMIC ACID METALLOPROTEASES INHIBITOR
Group Art Unit: 1625
Examiner: Ceila Chang
Attorney Docket Number 3124/4/US (formerly 116.6/US)

Declaration of Joseph J. McDonald, Ph.D.

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS,
SIR/MADAM:

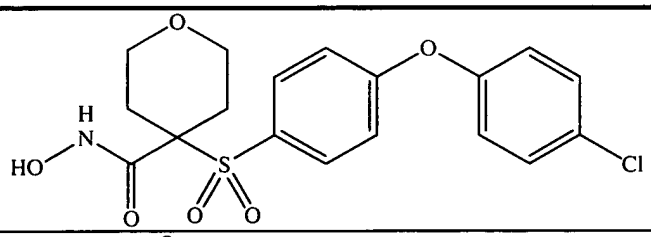
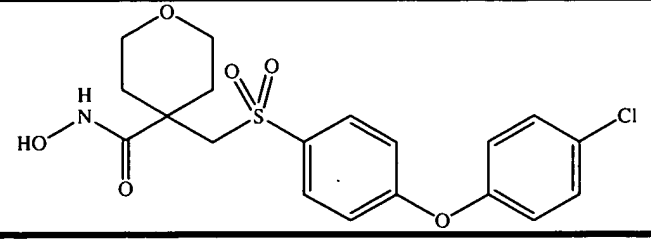
I, Dr. Joseph J. McDonald, declare the following:

1. I am a named inventor in the above-referenced patent application.

2. I am a group leader in computational chemistry at Pharmacia Corporation, the assignee of the above-referenced patent application.

3. Pharmacia has obtained the following data:

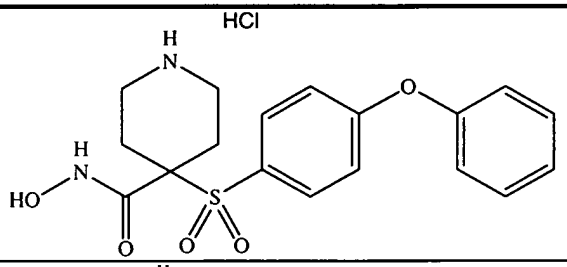
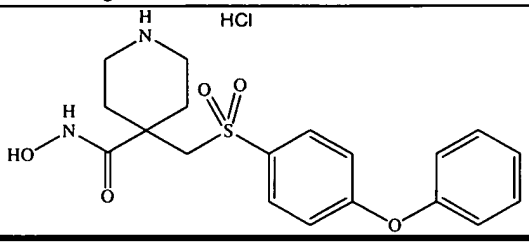
Comparison Between 1-Carbon and 2-Carbon Tetrahydropyranyl Compounds

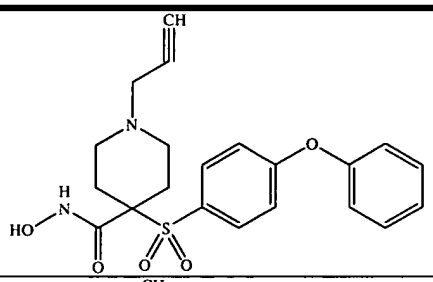
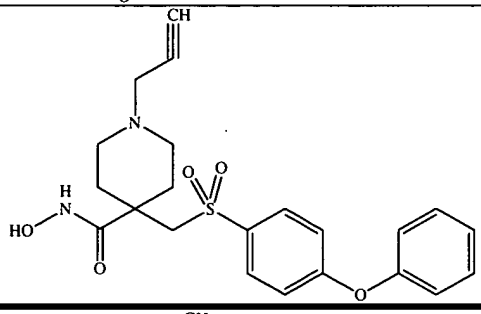
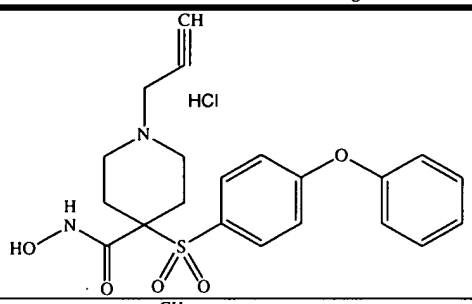
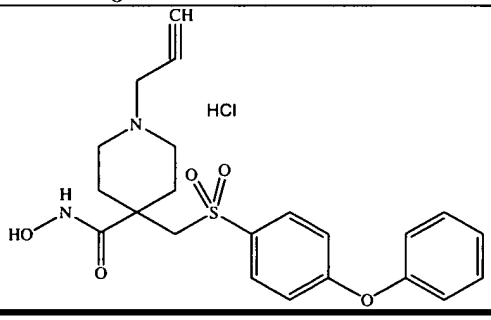
Compound	MMP-1 IC_{50}	MMP-13 IC_{50}
	435	0.15
	800	0.6

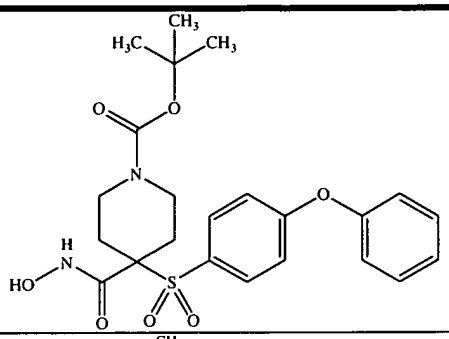
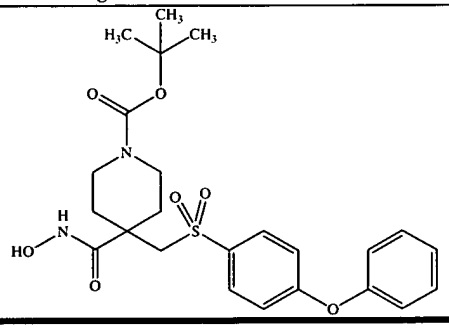
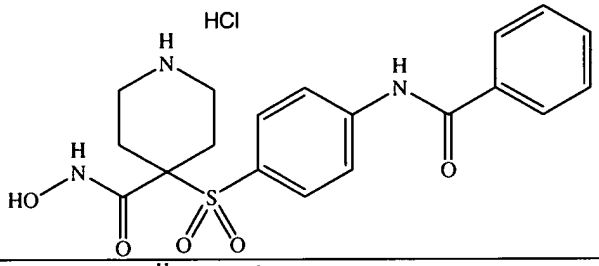
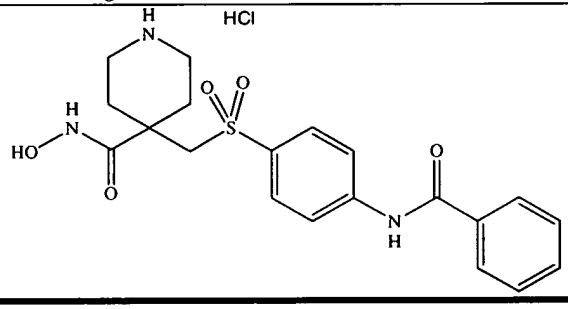
The above table compares a 1-carbon tetrahydropyranyl compound (*i.e.*, a compound, as described in the above-referenced patent application, having only one carbon between the sulfonyl and carbonyl) with a 2-carbon tetrahydropyranyl compound (*i.e.*, a compound having two carbons between the sulfonyl and carbonyl) that is otherwise identical. This is the only pair of such tetrahydropyranyl compounds that I could locate in the Pharmacia database at my disposal where the only difference between the compounds is a methylene group in the carbon linkage between the sulfonyl and carbonyl.

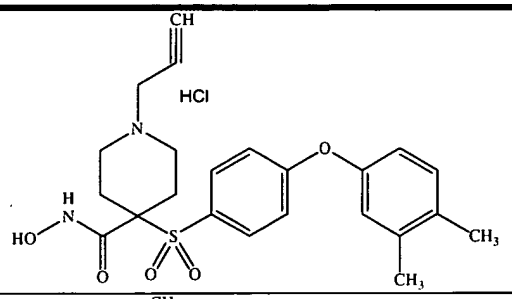
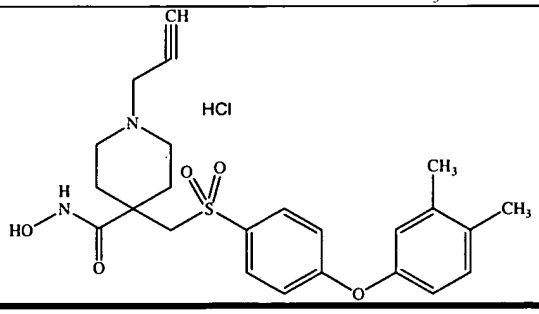
3. The following data related to piperidinyl compounds further demonstrates the observed effect of a one-carbon linker (rather than a two-carbon linker) between the sulfonyl and carbonyl:

Comparison Between 1-Carbon and 2-Carbon Piperidinyl Compounds

Compound or Salt	MMP-1 IC_{50}	MMP-13 IC_{50}
	1060 (average from 3 experiments)	0.33 (average from 3 experiments)
	2400	8.0

Compound or Salt	MMP-1 IC_{50}	MMP-13 IC_{50}
	327	0.25
	349	0.5
	239 (average from 3 experiments)	0.13 (average from 3 experiments)
	485	0.6

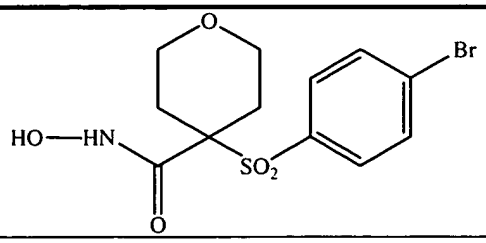
Compound or Salt	MMP-1 IC_{50}	MMP-13 IC_{50}
	1140	0.3
	475	0.2
	>10000	24.1
	>10000	243

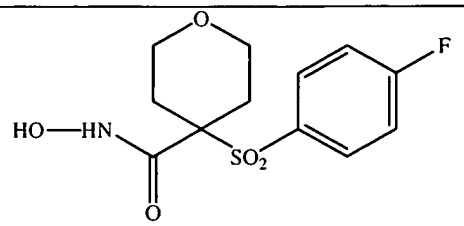
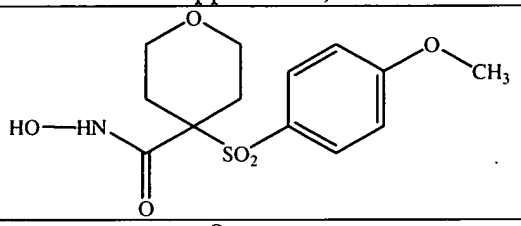
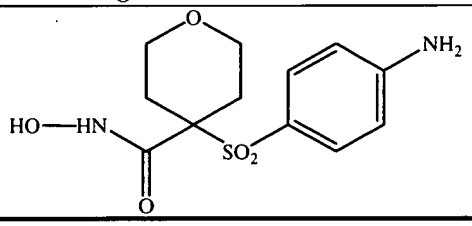
Compound or Salt	MMP-1 IC_{50}	MMP-13 IC_{50}
	7000	0.8
	7700	0.85

The above table compares 1-carbon piperidinyl compounds and salts (as described in the above-referenced patent application) with 2-carbon piperidinyl compounds and salts that are otherwise identical. These are the only pairs of such piperidinyl compounds and salts that I could locate in the Pharmacia database at my disposal where the only difference between the compounds is a methylene group in the carbon linkage between the sulfonyl and carbonyl.

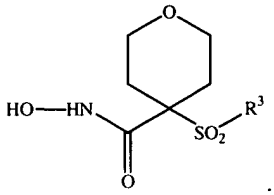
5. Pharmacia has obtained the following data:

Tetrahydropyranyl Compounds with a Single-Ring Substituent on the Sulfonyl

Compound	MMP-1 Inhibition IC50 (nM)	MMP-13 Inhibition IC50 (nM)
	200	7.0

 (Example 66 in the above-referenced patent application)	1600	268
	1000	23.0
	8000	30

The above table shows MMP inhibition data for tetrahydropyranyl compounds having a single-ring substituent on the sulfonyl. The compounds in the above table are the only such compounds that I could locate in the Pharmacia database at my disposal where the compound corresponds in structure the following formula with R^3 being the substituent on the sulfonyl:

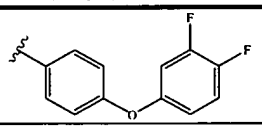
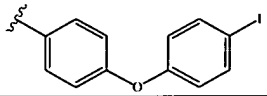
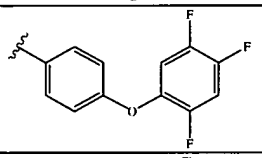
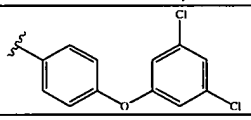
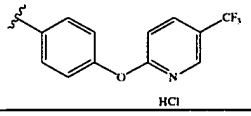
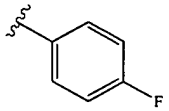
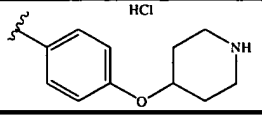


6. The MMP inhibition data in the above tables was obtained by the method described in the above-referenced patent application.

7. Dividing the MMP-1 inhibition IC_{50} value by the MMP-13 inhibition IC_{50} value provides a relative measure of the selectivity of a compound or salt.

8. Based on the Pharmacia database at my disposal, it is my belief that the MMP inhibition IC_{50} values on page 874 of the above-referenced patent application should be as follows for the compounds of Examples 56, 57, 58, 59, 59(b), 66, and 67:

Corrections to Data in Applicants' Specification

Example Number	Structure wherein R^3 is:	MMP-1 IC_{50}	MMP-2 IC_{50}	MMP-13 IC_{50}
56		1200	0.1	0.3
57		1500	<0.1	0.15
58		1200	<0.1	0.2
59		>10000	83	30
59(b)		>10000	130	180
66		1600	239	268
67		>10000	9000	6000

9. All statements made in this declaration of my own knowledge are tra and all statements made on information and belief are believed to be true; and further, these statements have been made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. §1001, and that such willful, false statements may jeopardize the validity of the above-referenced patent application or any patent issuing thereon.

11/2/2001
Date

Joseph J. McDonald